P&S Mobile Genomics

Lecture 9: GRIM-Filter

Jeremie S. Kim

ETH Zurich

Fall 2022

13 December 2022

SAFARI

ETH zürich

GRIM-Filter:

Fast seed location filtering in DNA read mapping using processing-in-memory technologies

Jeremie S. Kim,
Damla Senol Cali, Hongyi Xin, Donghyuk Lee,
Saugata Ghose, Mohammed Alser, Hasan Hassan,
Oguz Ergin, Can Alkan, and Onur Mutlu

SAFARI

Carnegie Mellon

TOBB
UNIVERSITY OF
ECONOMICS AND TECHNOLOGY

ETH zürich

Executive Summary

- **Genome Read Mapping** is a very important problem and is the first step in genome analysis
- Read Mapping is an **approximate string matching** problem
  - Find the best fit of 100 character strings into a 3 billion character dictionary
  - **Alignment** is currently the best method for determining the similarity between two strings, but is **very expensive**
- We propose an algorithm called **GRIM-Filter**
  - Accelerates read mapping by reducing the number of required alignments
  - GRIM-Filter can be accelerated using **processing-in-memory**
    - Adds simple logic into **3D-Stacked memory**
    - Uses high internal memory bandwidth to perform parallel filtering
- GRIM-Filter with processing-in-memory delivers a **3.7x speedup**

GRIM-Filter Outline

1. Motivation and Goal

2. Background Read Mappers

   a. Hash Table Based

   b. Hash Table Based with Filter

3. Our Proposal: GRIM-Filter

4. Mapping GRIM-Filter to 3D-Stacked Memory

5. Results

6. Conclusion

Motivation and Goal

- **Sequencing**: determine the [A,C,G,T] series in DNA strand
- Today's machines sequence short strands (**reads**)
  - Reads are on the order of 100 – 20k base pairs (**bp**)
  - The human genome is approximately 3 billion bp
- Therefore genomes are cut into reads, which are sequenced independently, and then reconstructed
  - **Read mapping** is the first step in analyzing someone's genome to detect predispositions to diseases, personalize medicine, etc.
- **Goal**: We want to **accelerate** end-to-end performance of **read mapping**

GRIM-Filter Outline

1. Motivation and Goal
2. **Background: Read Mappers**
   - **a.** Hash Table Based
   - **b.** Hash Table Based with Filter
3. Our Proposal: GRIM-Filter
4. Mapping GRIM-Filter to 3D-Stacked Memory
5. Results
6. Conclusion

Background: Read Mappers

We now have **sequenced reads** and want a **full genome**

We map **reads** to a known **reference genome** (>99.9% similarity across humans) with some minor errors allowed

Because of high similarity, long sequences in **reads** perfectly match in the **reference genome**

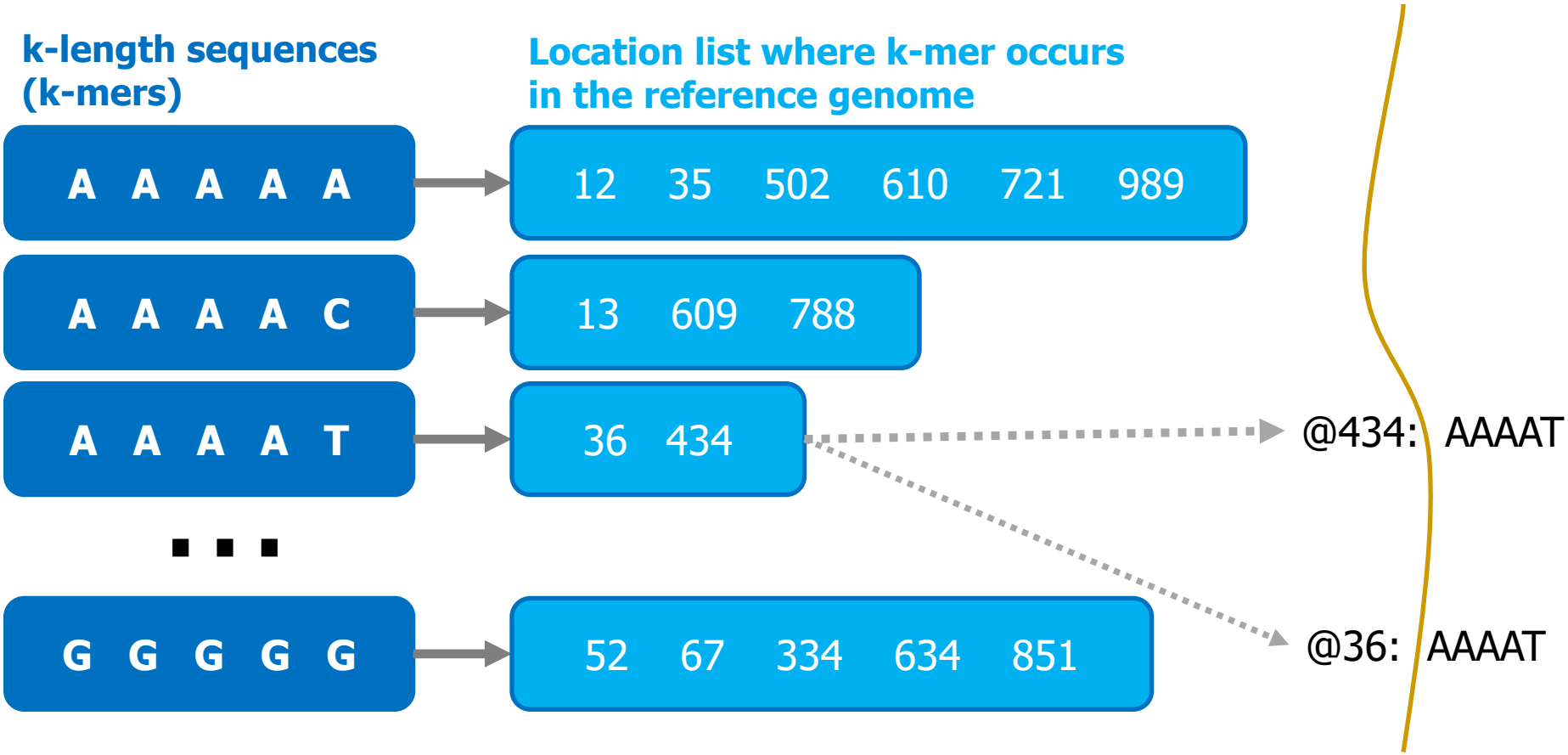
We can use a hash table to help quickly map the reads!

GRIM-Filter Outline

1. Motivation and Goal
2. **Background: Read Mappers**
   - **a. Hash Table Based**
   - **b.** Hash Table Based with Filter
3. Our Proposal: GRIM-Filter
4. Mapping GRIM-Filter to 3D-Stacked Memory
5. Results
6. Conclusion

Generating Hash Tables

To map any reads, generate a **hash table** per **reference genome.**



We can query the table with substrings from reads to quickly find a list of possible mapping locations

Hash Tables in Read Mapping

Read Sequence (100 bp)

99.9% of locations result in a mismatch

Hash Table

Reference Genome

We want to filter these out so we do not waste time trying to align them

Location Filtering

- **Alignment** is expensive and requires the use of $O(n^2)$ dynamic programming algorithm
  - We need to align millions to billions of reads
- M
  - f
  - 1
  - 2

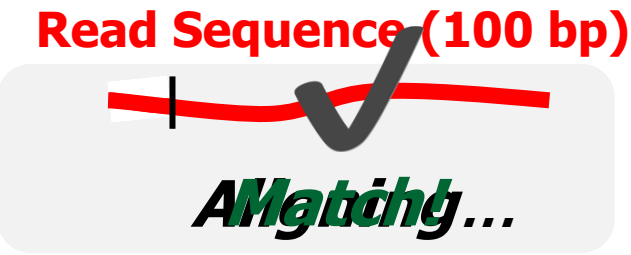
Our goal is to accelerate read mapping by improving the filtering step

- Both methods are used by mappers today, but filtering has replaced alignment as the bottleneck **[Xin+, BMC Genomics 2013]**

GRIM-Filter Outline

1. Motivation and Goal
2. **Background: Read Mappers**
   - a. Hash Table Based
   - **b. Hash Table Based with Filter**
3. Our Proposal: GRIM-Filter
4. Mapping GRIM-Filter to 3D-Stacked Memory
5. Results
6. Conclusion

Hash Tables in Read Mapping



False Negative

Hash Table

37 140
894 1203
1564

Reference Genome

Filter

GRIM-Filter Outline

1. Motivation and Goal
2. Background: Read Mappers
   - a. Hash Table Based
   - b. Hash Table Based with Filter
3. **Our Proposal: GRIM-Filter**
4. Mapping GRIM-Filter to 3D-Stacked Memory
5. Results
6. Conclusion

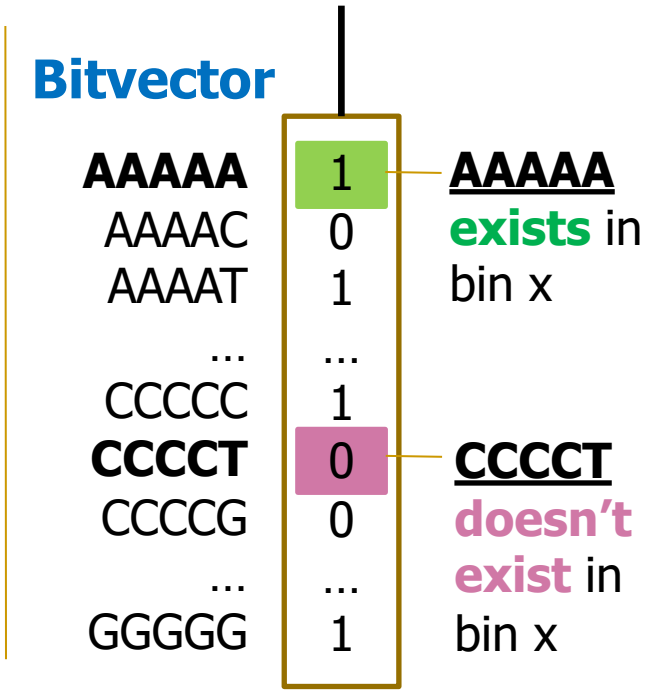
Our Proposal: GRIM-Filter

1. **Data Structures: Bins & Bitvectors**
2. Checking a Bin
3. Integrating GRIM-Filter into a Mapper

GRIM-Filter: Bins

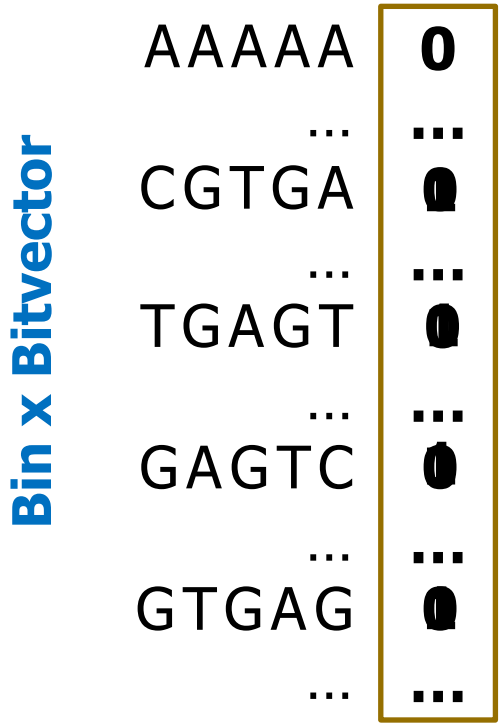
- We partition the genome into large sequences (**bins**).

- Represent each bin with a **bitvector** that holds the occurrence of all permutations of a small string (**token**) in the bin
- To account for matches that straddle bins, we employ overlapping bins
  - A read will now always completely fall within a single bin

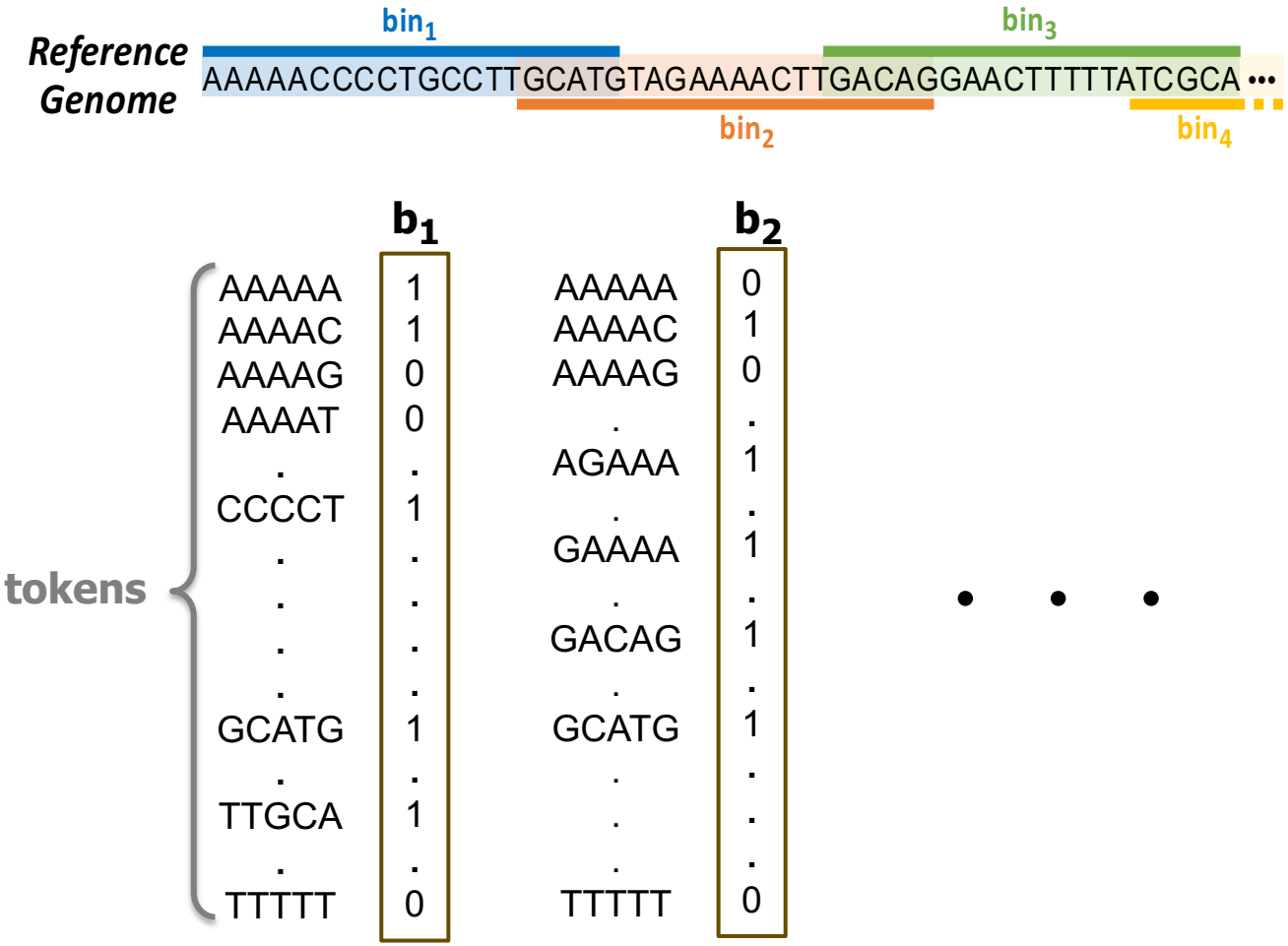


GRIM-Filter: Bitvectors

Bin x



GRIM-Filter: Bitvectors



Storing all bitvectors requires $4^n * t$ bits in memory, where t = number of bins.

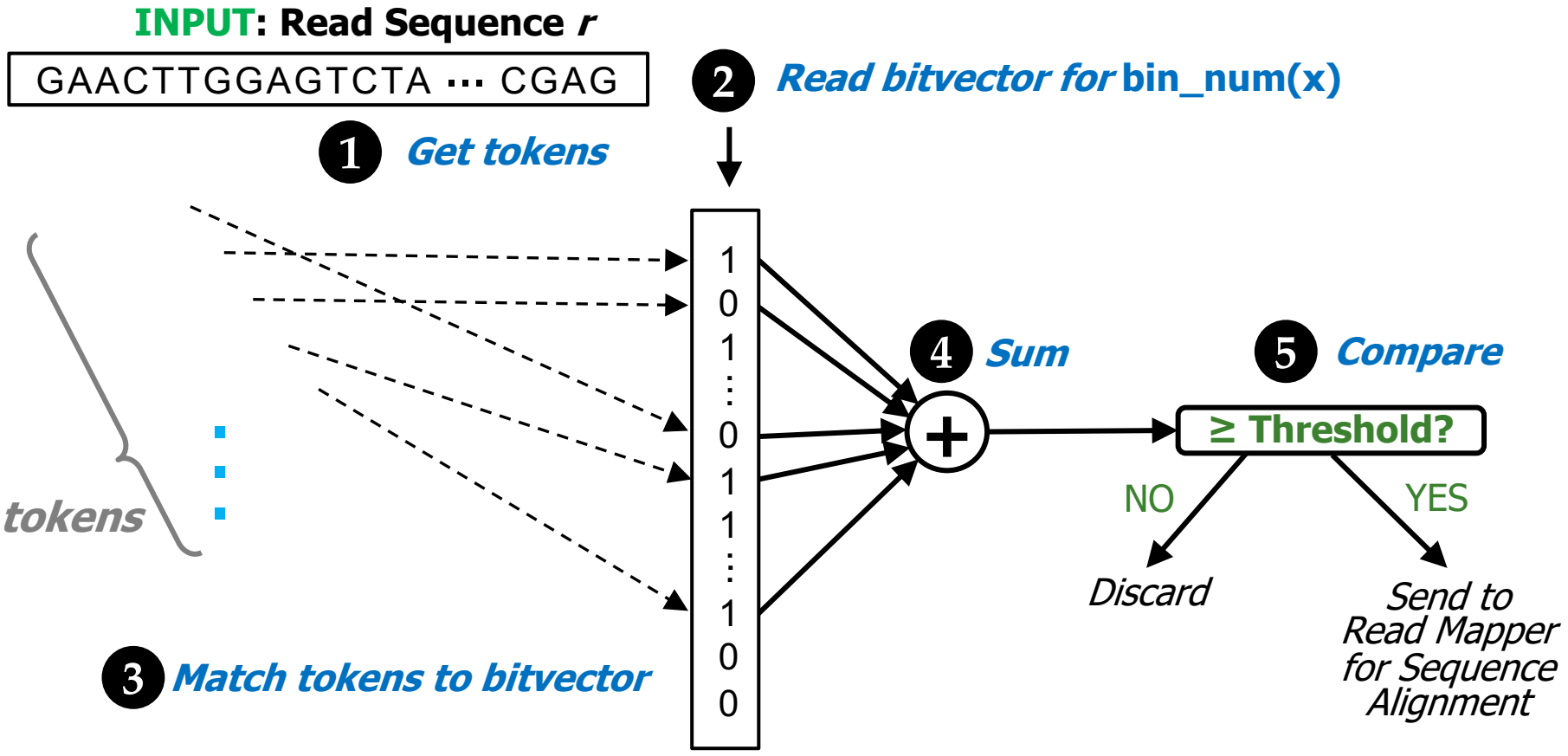
For **bin size** ~200, and **n** = 5, **memory footprint** ~3.8 GB

Our Proposal: GRIM-Filter

1. Data Structures: Bins & Bitvectors
2. **Checking a Bin**
3. Integrating GRIM-Filter into a Mapper

GRIM-Filter: Checking a Bin

How GRIM-Filter determines whether to **discard** potential match locations in a given bin **prior** to alignment



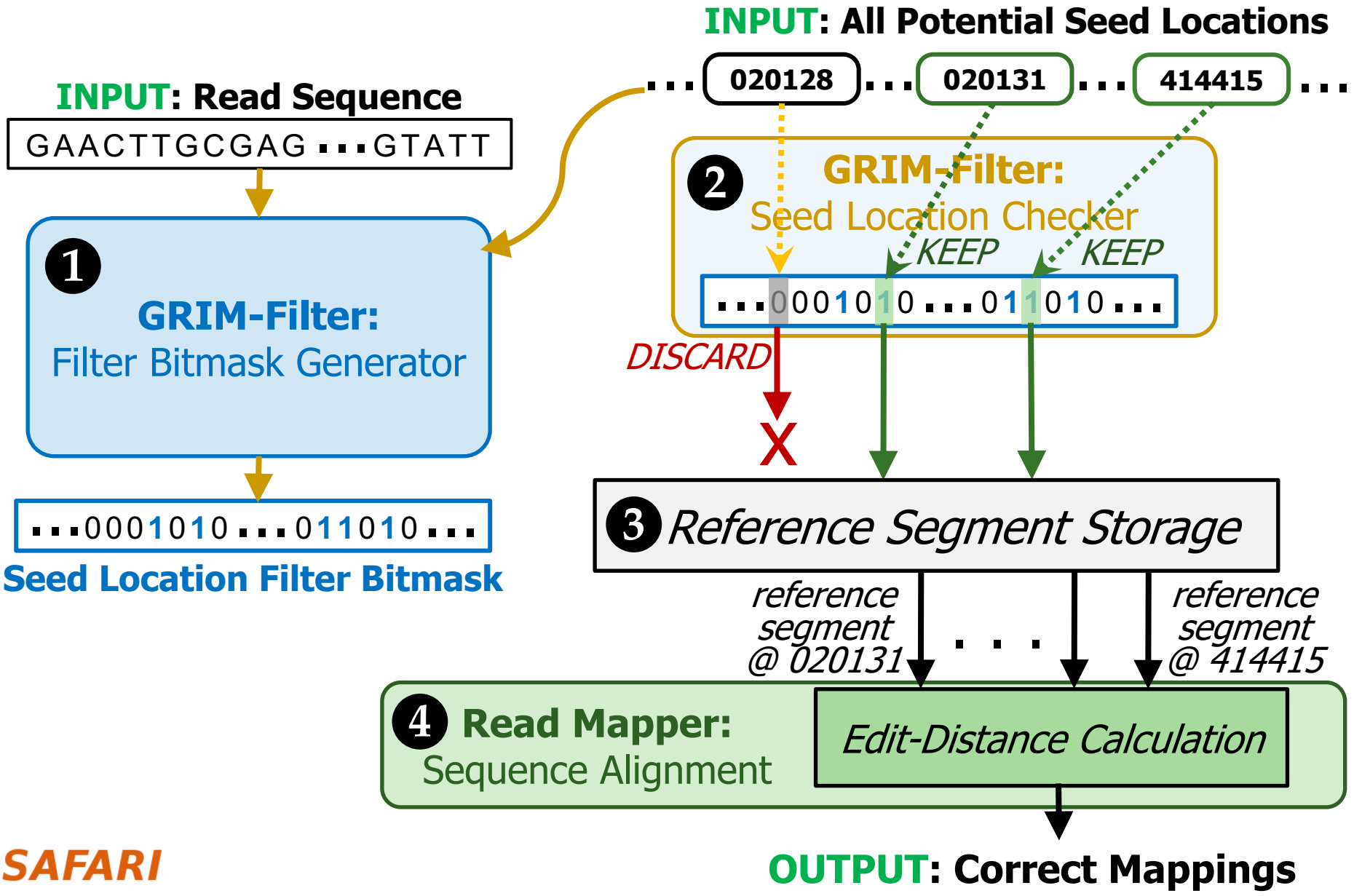
Our Proposal: GRIM-Filter

1. Data Structures: Bins & Bitvectors
2. Checking a Bin
3. Integrating GRIM-Filter into a Mapper

Our Proposal: GRIM-Filter

1. Data Structures: Bins & Bitvectors
2. Checking a Bin
3. **Integrating GRIM-Filter into a Mapper**

Integrating GRIM-Filter into a Read Mapper



SAFARI

GRIM-Filter Outline

1. Motivation and Goal
2. Background: Read Mappers
    a. Hash Table Based
    b. Hash Table Based with Filter
3. Our Proposal: GRIM-Filter
4. Mapping GRIM-Filter to 3D-Stacked Memory
5. Results
6. Conclusion

Key Properties of GRIM-Filter

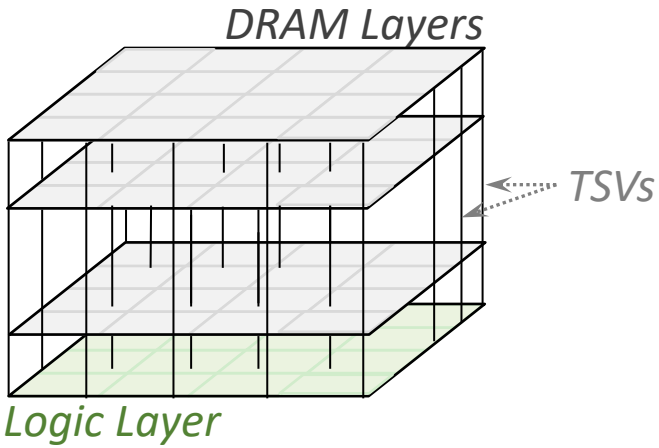
1. **Simple Operations**:
   - To check a given bin, find the **sum** of all bits corresponding to each token in the read
   - **Compare** against threshold to determine whether to align

2. **Highly Parallel**: Each bin is operated on independently and there are many many bins

3. **Memory Bound**: Given the frequent accesses to the large bitvectors, we find that GRIM-Filter is memory bound

These properties together make GRIM-Filter a good algorithm to be run in 3D-Stacked DRAM

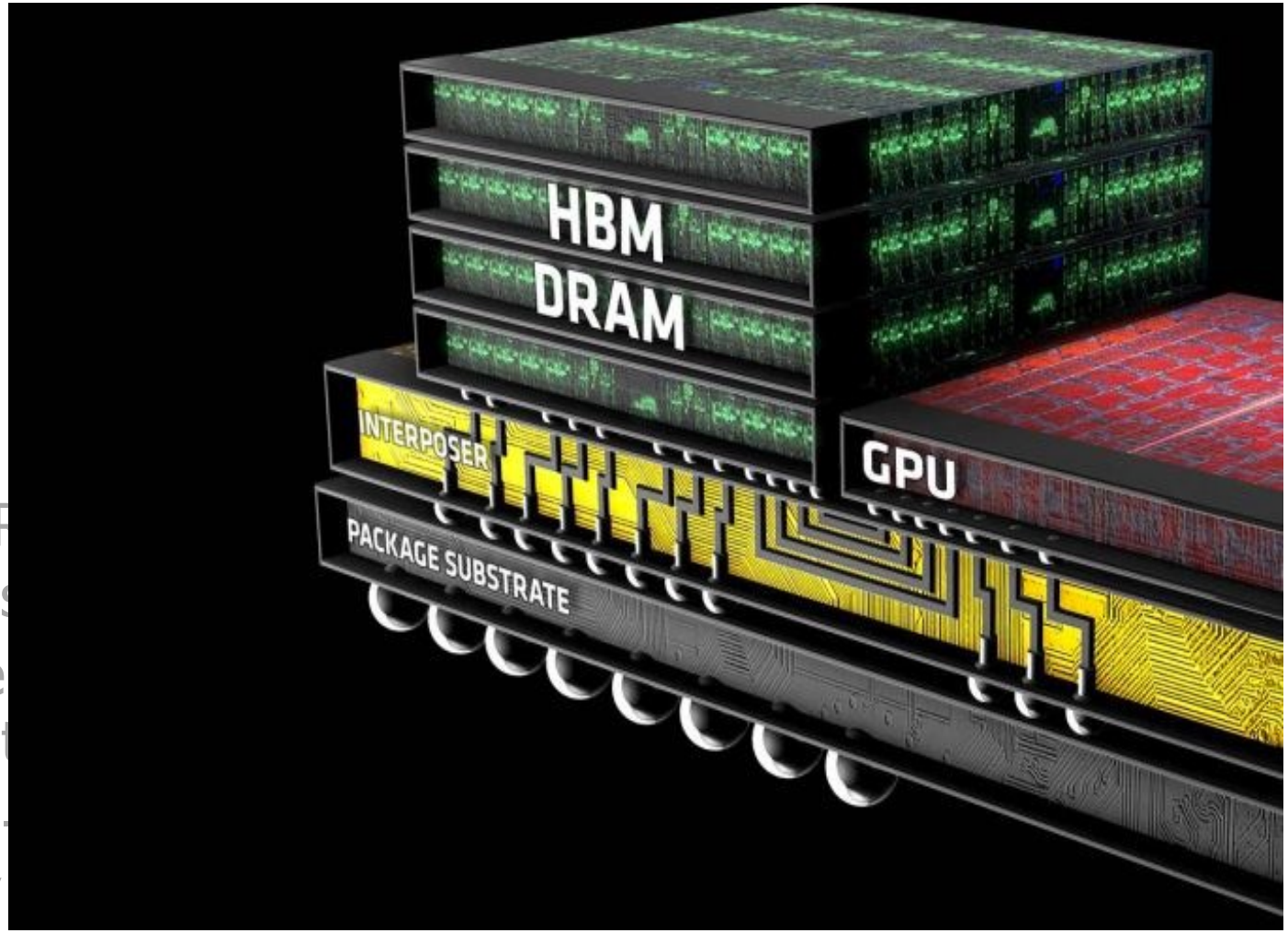
3D-Stacked Memory



- 3D-Stacked DRAM architecture has **extremely high bandwidth** as well as a stacked customizable logic layer
  - Logic Layer enables **Processing-in-Memory**, offloading computation to this layer and alleviating the memory bus
  - Embed GRIM-Filter operations into **DRAM logic layer** and appropriately distribute bitvectors throughout memory

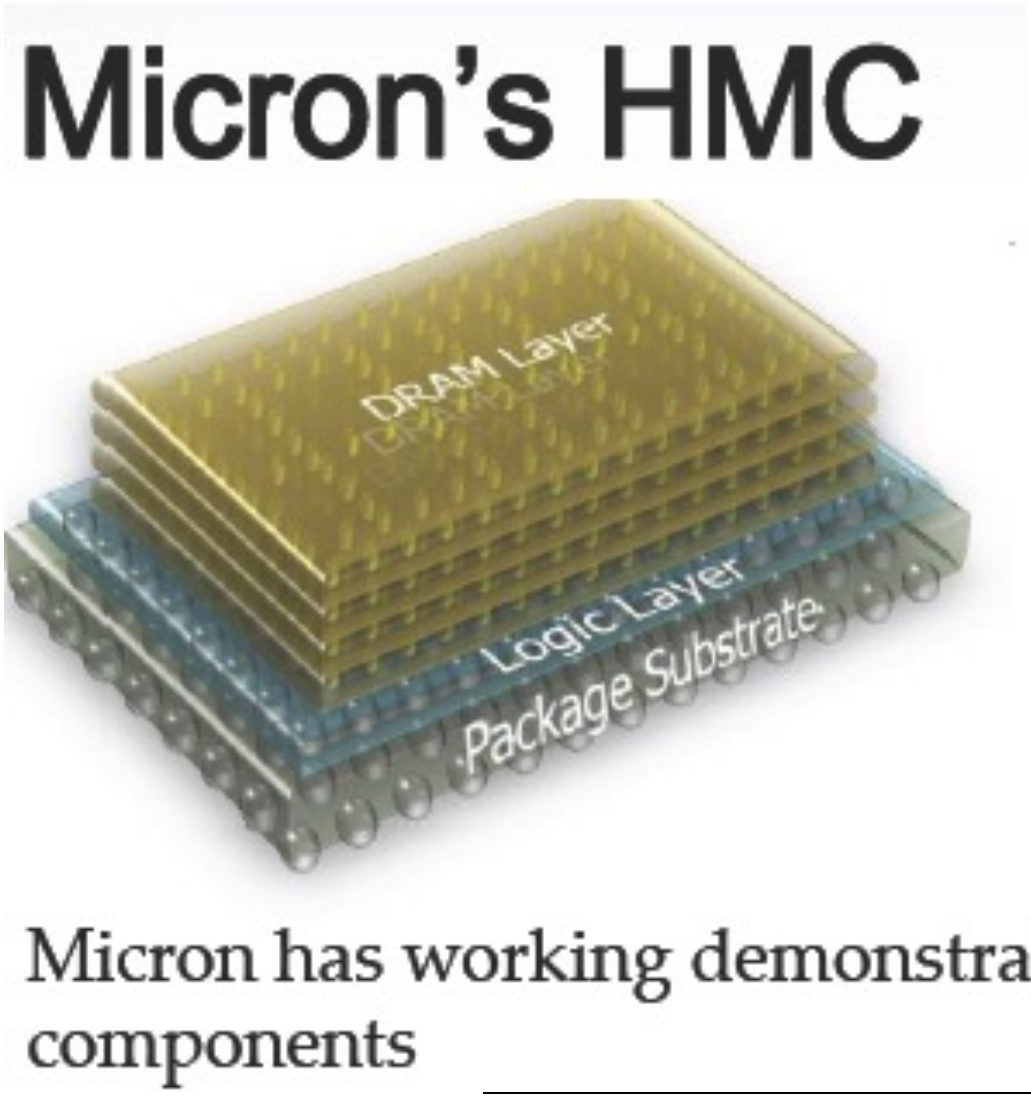
3D-Stacked Memory

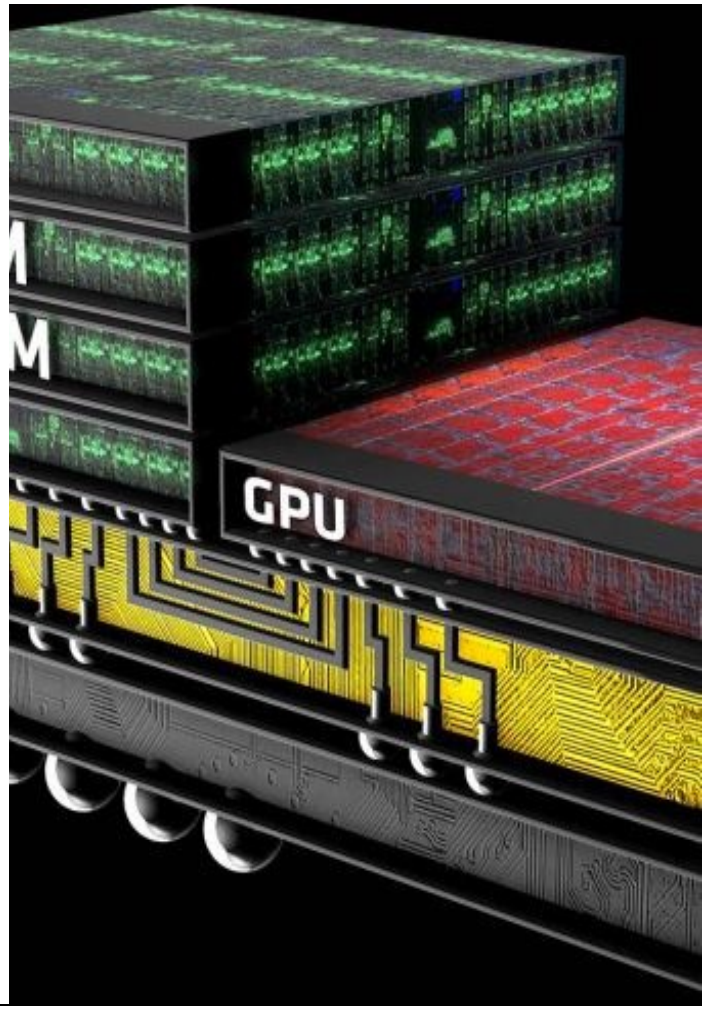
- 3D-Stacked DR
  bandwidth as
  - Logic Layer e
    computation t
  - Embed GRIM-
    appropriately



http://i1-news.softpedia-static.com/images/news2/Micron-and-Samsung-Join-Force-to-Create-Next-Gen-Hybrid-Memory-2.png

3D-Stacked Memory

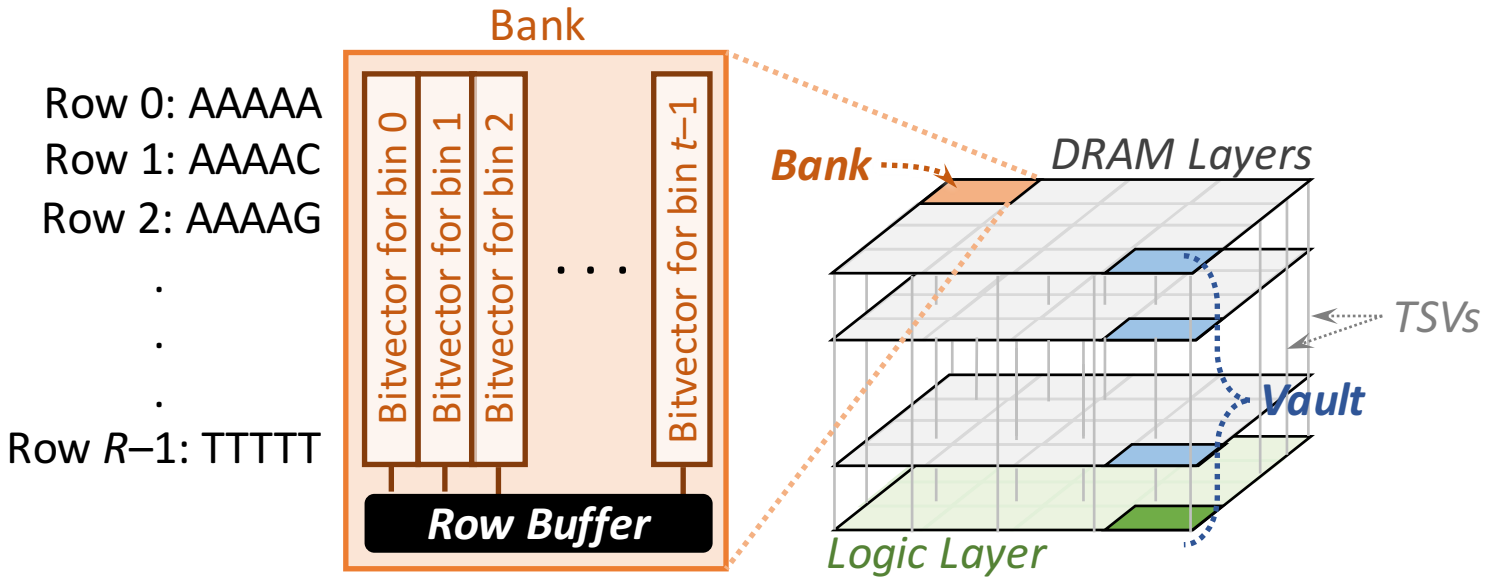




http://images.anandtech.com/doci/9266/HBMCar_678x452.jpg

http://i1-news.softpedia-static.com/images/news2/Micron-and-Samsung-Join-Force-to-Create-Next-Gen-Hybrid-Memory-2.png

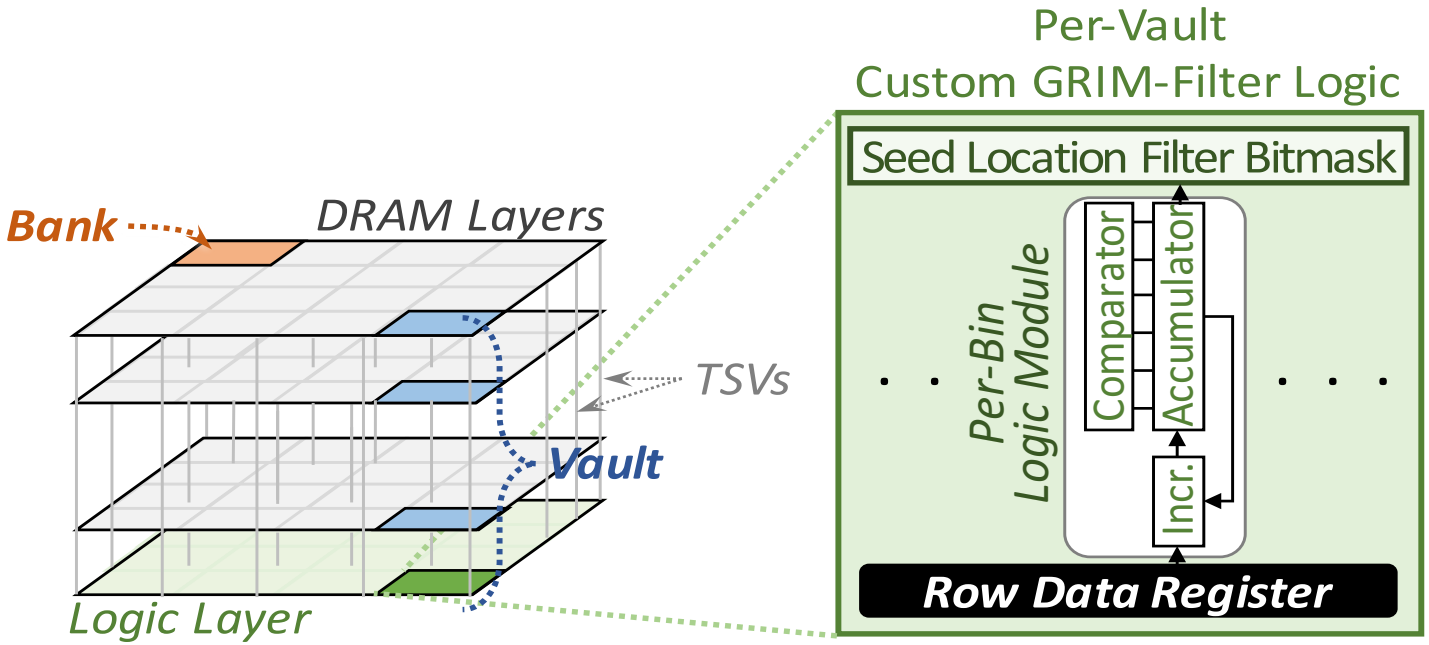
GRIM-Filter in 3D-Stacked DRAM



- Each DRAM layer is organized as an array of **banks**
  - A **bank** is an array of cells with a row buffer to transfer data

- The layout of bitvectors in a bank enables filtering many bins in parallel

GRIM-Filter in 3D-Stacked DRAM



- Customized logic for accumulation and comparison per genome segment
  - Low area overhead, simple implementation
  - For HBM2, we use 4096 incrementer LUTs, 7-bit counters, and comparators in logic layer

Details are in the paper

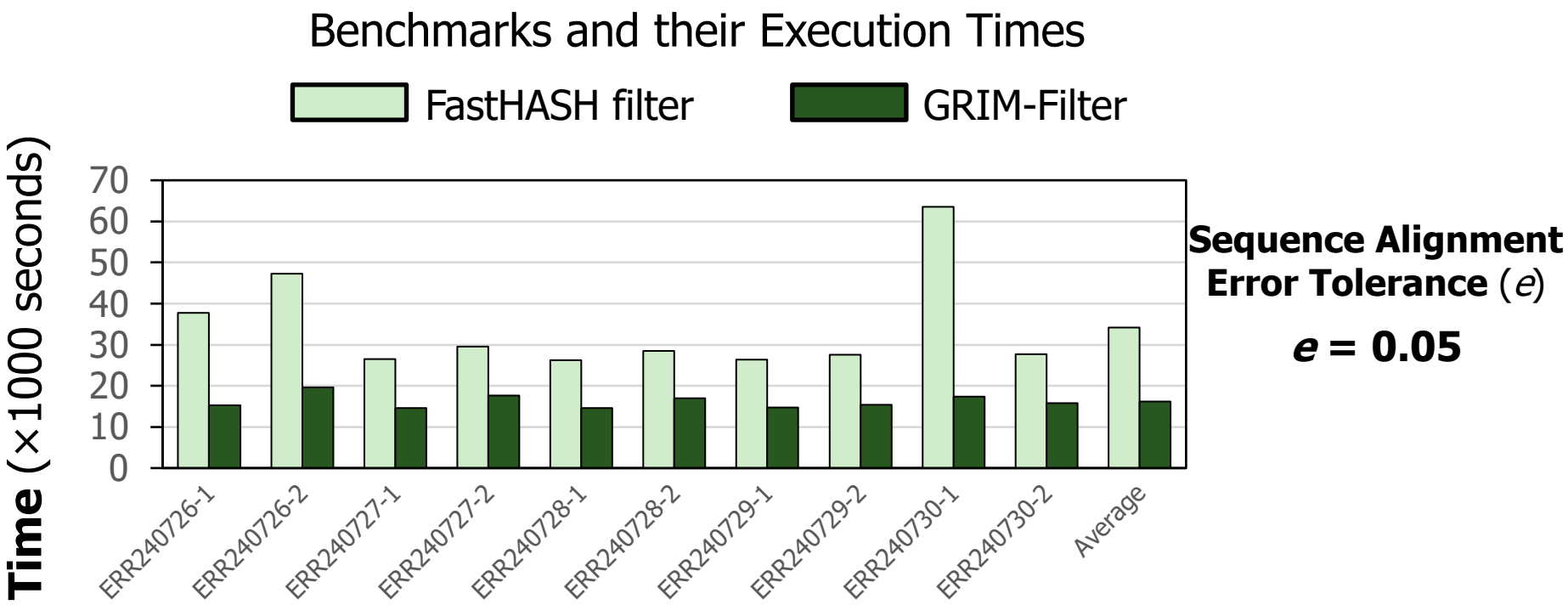
GRIM-Filter Outline

1. Motivation and Goal
2. Background: Read Mappers
   - a. Hash Table Based
   - b. Hash Table Based with Filter
3. Our Proposal: GRIM-Filter
4. Mapping GRIM-Filter to 3D-Stacked Memory
5. **Results**
6. Conclusion

Methodology

- Performance simulated using an in-house 3D-Stacked DRAM simulator
- Evaluate 10 real read data sets (From the 1000 Genomes Project)
  - Each data set consists of 4 million reads of length 100
- Evaluate two key metrics
  - Performance
  - False negative rate
    - The fraction of locations that pass the filter but result in a mismatch
- Compare against a state-of-the-art filter, FastHASH **[Xin+, BMC Genomics 2013]** when using mrFAST, but **GRIM-Filter can be used with ANY read mapper**

GRIM-Filter Performance

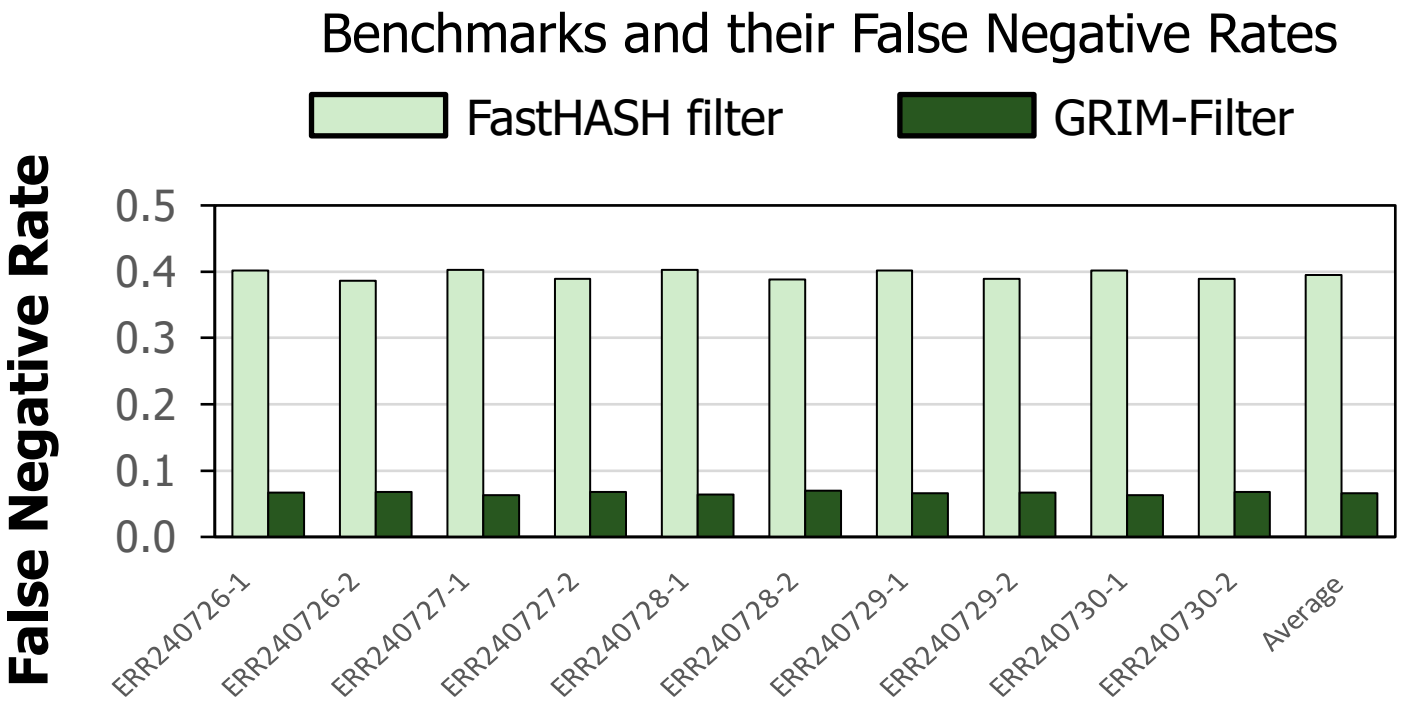


1.8x-3.7x performance benefit across real data sets

2.1x average performance benefit

GRIM-Filter gets performance due to its hardware-software co-design

GRIM-Filter False Negative Rate



Sequence Alignment Error Tolerance (*e*)

***e* = 0.05**

5.6x-6.4x False Negative reduction across real data sets

6.0x average reduction in False Negative Rate

GRIM-Filter utilizes more information available in the read to filter

Other Results in the Paper

- Sensitivity of execution time and false negative rates to error tolerance of string matching
- Read mapper execution time breakdown
- Sensitivity studies on the filter
  - Token Size
  - Bin Size
  - Error Tolerance

GRIM-Filter Outline

1. Motivation and Goal
2. Background: Read Mappers
   - a. Hash Table Based
   - b. Hash Table Based with Filter
3. Our Proposal: GRIM-Filter
4. Mapping GRIM-Filter to 3D-Stacked Memory
5. Results
6. **Conclusion**

Conclusion

We propose an in-memory filtering algorithm to accelerate end-to-end read mapping by reducing the number of required alignments

Key ideas:

- Introduce a **new representation** of coarse-grained segments of the reference genome
- Use **massively-parallel in-memory operations** to identify read presence within each coarse-grained segment

Key contributions and results:

- Customized filtering algorithm for 3D-Stacked DRAM
- Compared to the previous best filter
  - We observed 1.8x-3.7x read mapping speedup
  - We observed 5.6x-6.4x fewer false negatives

GRIM-Filter is a universal filter that can be applied to any read mapper

GRIM-Filter:

Fast seed location filtering in DNA read mapping using processing-in-memory technologies

Jeremie S. Kim,
Damla Senol Cali, Hongyi Xin, Donghyuk Lee,
Saugata Ghose, Mohammed Alser, Hasan Hassan,
Oguz Ergin, Can Alkan, and Onur Mutlu

SAFARI

Carnegie Mellon

TOBB
UNIVERSITY OF
ECONOMICS AND TECHNOLOGY

ETH zürich

P&S Mobile Genomics

Lecture 9: GRIM-Filter

Jeremie S. Kim

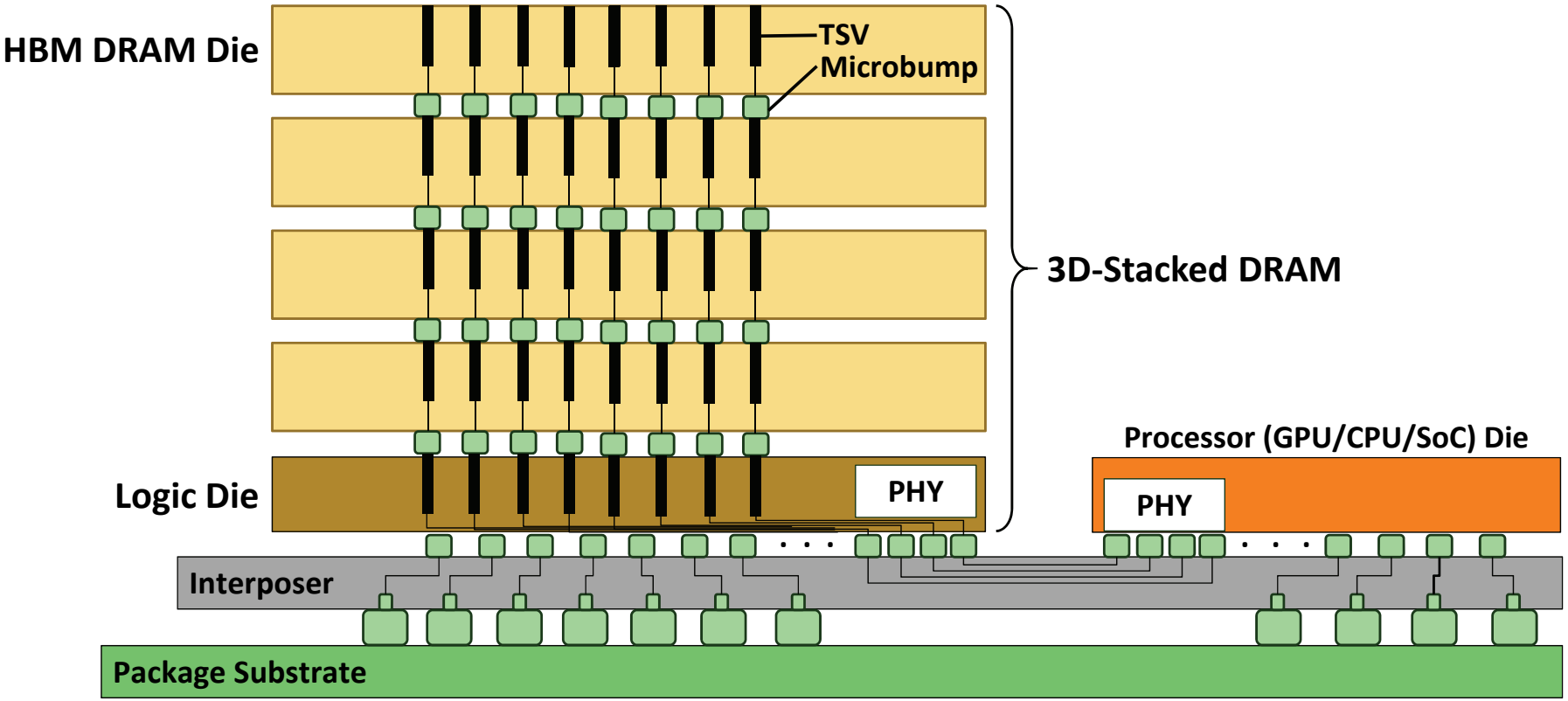
ETH Zurich

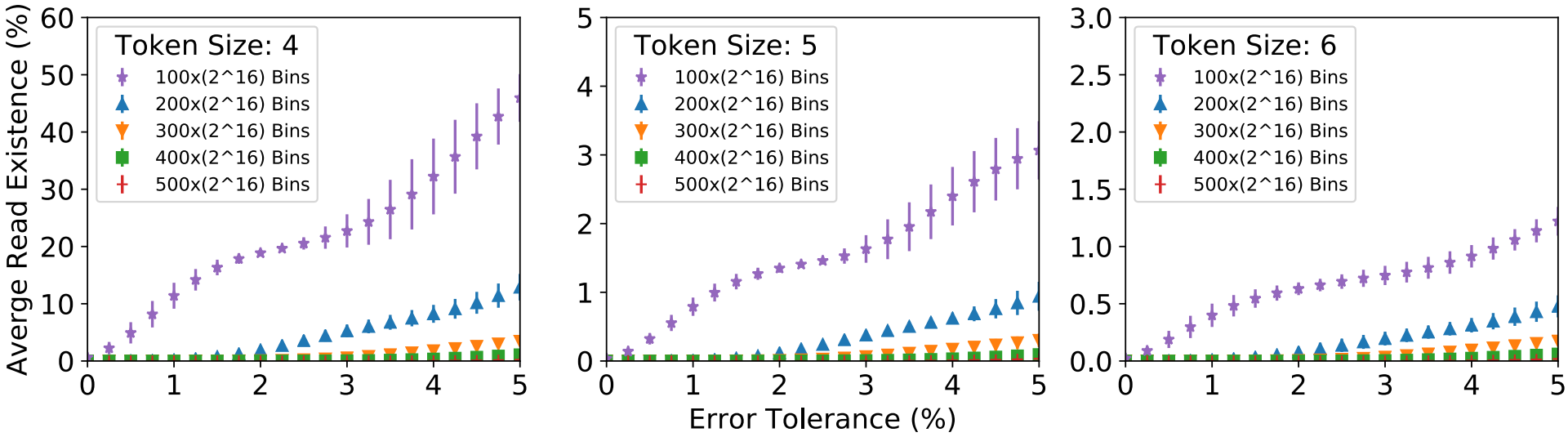
Fall 2022

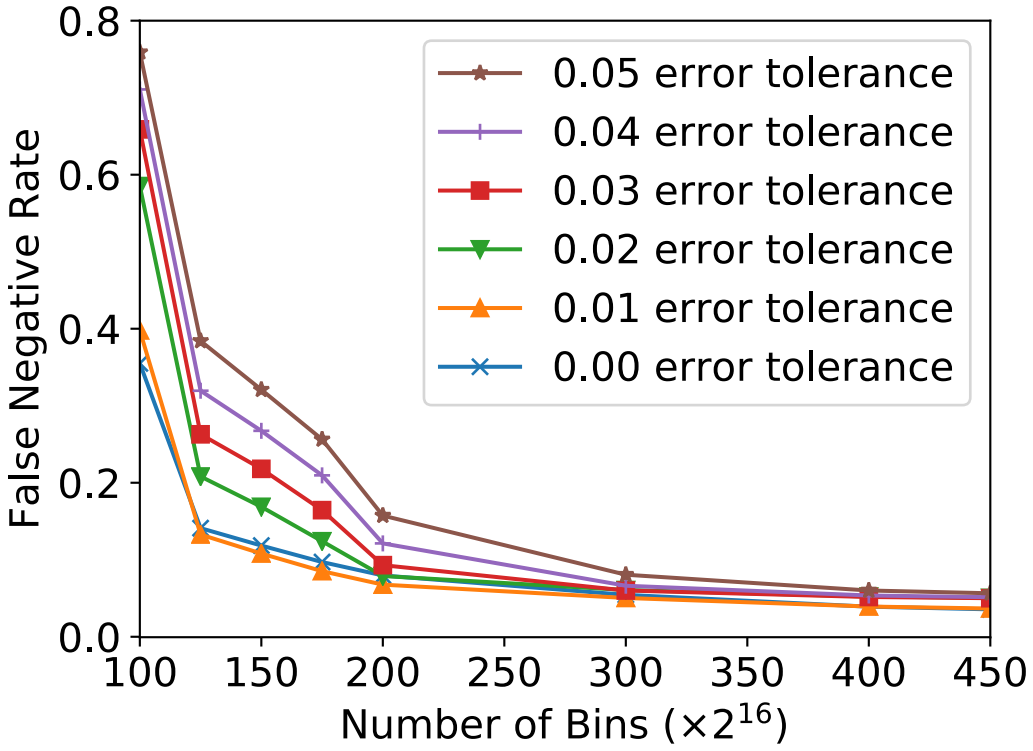
13 December 2022

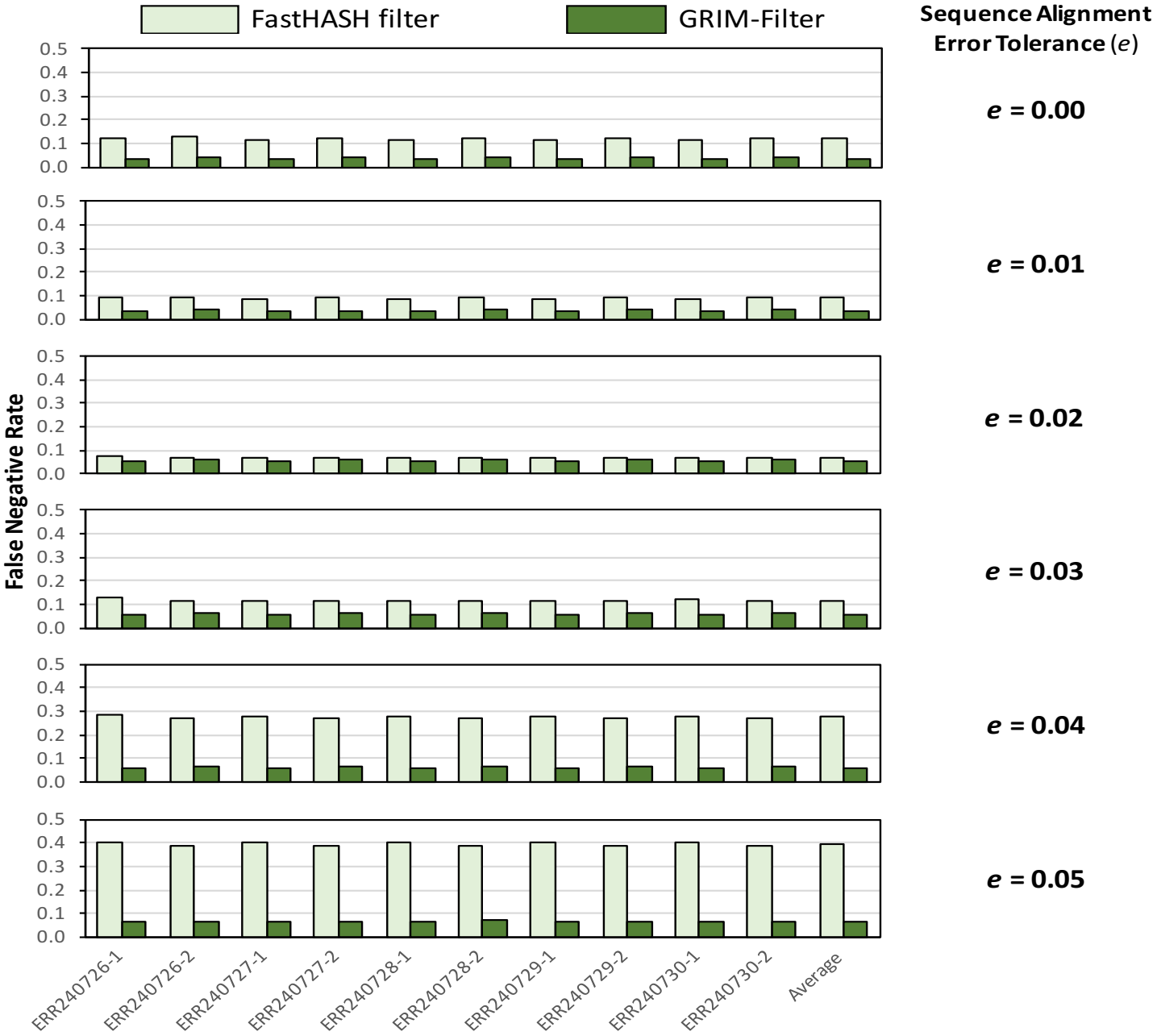
SAFARI

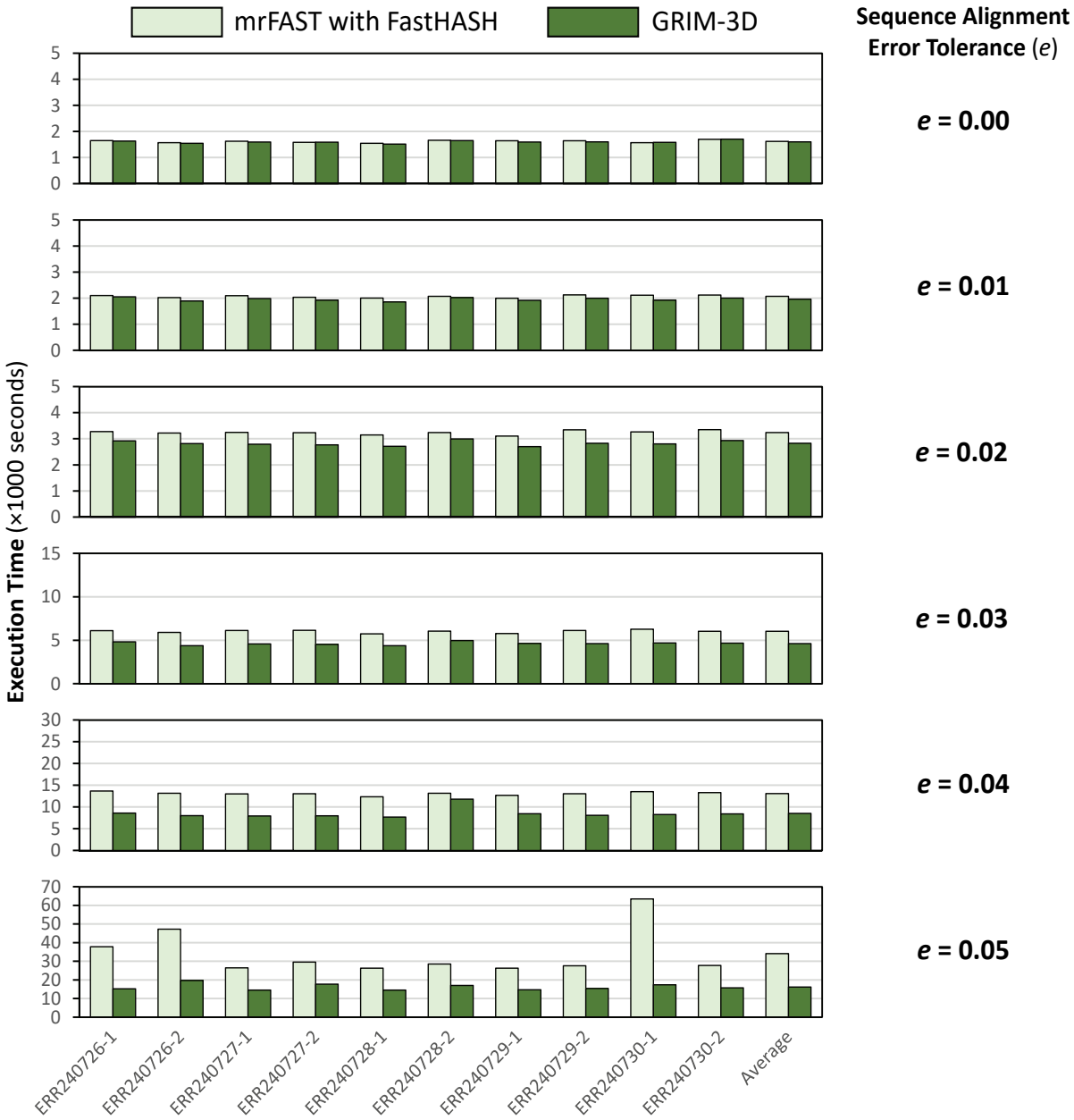
ETH zürich


HBM DRAM Die
TSV
Microbump
3D-Stacked DRAM
Logic Die
PHY
Processor (GPU/CPU/SoC) Die
PHY
Interposer
Package Substrate


Averge Read Existence (%)
Token Size: 4
100x(2^16) Bins
200x(2^16) Bins
300x(2^16) Bins
400x(2^16) Bins
500x(2^16) Bins
Token Size: 5
Token Size: 6
Error Tolerance (%)


0.8
0.6
0.4
0.2
0.0
False Negative Rate
100
150
200
250
300
350
400
450
Number of Bins (×2^16)
0.05 error tolerance
0.04 error tolerance
0.03 error tolerance
0.02 error tolerance
0.01 error tolerance
0.00 error tolerance


FastHASH filter
GRIM-Filter
Sequence Alignment Error Tolerance (e)
False Negative Rate
0.5
0.4
0.3
0.2
0.1
0.0
e = 0.00
e = 0.01
e = 0.02
e = 0.03
e = 0.04
e = 0.05
ERR240726-1
ERR240726-2
ERR240727-1
ERR240727-2
ERR240728-1
ERR240728-2
ERR240729-1
ERR240729-2
ERR240730-1
ERR240730-2
Average


mrFAST with FastHASH
GRIM-3D
Sequence Alignment Error Tolerance (e)
e = 0.00
e = 0.01
e = 0.02
e = 0.03
e = 0.04
e = 0.05
Execution Time (×1000 seconds)
ERR240726-1
ERR240726-2
ERR240727-1
ERR240727-2
ERR240728-1
ERR240728-2
ERR240729-1
ERR240729-2
ERR240730-1
ERR240730-2
Average

GRIM-Filter: Error Tolerance

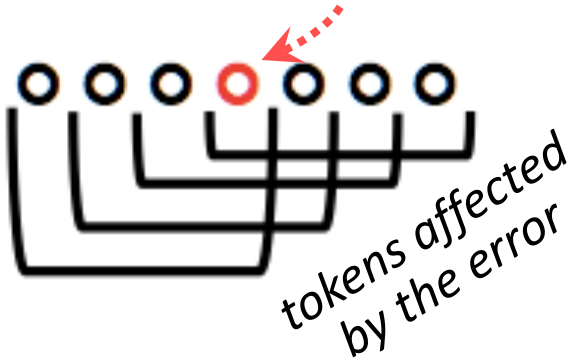
total number of tokens in a read

$$\text{Threshold} = \text{read\_length} - (n-1) - n \times \lceil \text{read\_length} \times e \rceil$$

maximum number of tokens that could contain errors

number of errors allowed per read

single substitution error



one substitution error affects four tokens when n = 4

GRIM-Filter can support different error tolerances by simply changing the threshold value

More details in the paper